IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.
Koike *et al.*	Art Unit: To Be Assigned
Appl. No.: 10/662,820	Examiner: To Be Assigned
Filed: September 16, 2003	Atty. Docket: 1089.0410001/TUM
For: **Quinone-based Therapeutic Agent for Hepatopathy**	

Submission of Accurate Translation of Provisional Application Under 37 C.F.R. § 1.78(a)(5)

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

In compliance with 37 C.F.R. § 1.78(a)(5), submitted herewith is a translation of Applicants' U.S. provisional application priority document, U.S. Appl. No. 60/410,793. The translation is accurate and a Statement Verifying the Accuracy of the English Translation of Japanese Patent Application is filed herewith. This submission is being made within the later of four months from the actual filing date of the above-captioned nonprovisional application or sixteen months from the filing date of the provisional application. Prompt acknowledgment of this submission is respectfully requested.

In addition, Applicants file herewith a Statement of Accuracy with regard to the English translation of the Japanese language nonprovisional U.S. Appl. No. 10/662,820 filed on September 16, 2003, as well as a copy of the English translation of U.S. Appl. No. 10/662,820.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Teresa U. Medler
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Date: January 12, 2004

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Provisional Patent Application of:
Yukihiro KOIKE, et al.

Provisional Patent Application No. 60/410,793 — Group Art Unit:

Filed: September 16, 2002 — Examiner: Not Yet Assigned

For: QUINONE-BASED THERAPEUTIC AGENT FOR HEPATOPATHY

STATEMENT VERIFYING THE ACCURACY OF THE ENGLISH TRANSLATION OF JAPANESE PATENT APPLICATION

Commissioner for Patents
Washington, DC 20231

Dear Sir:

The undersigned hereby declares and attests that the attached English translation of related United States provisional patent application no.60/410,793 filed in Japanese language on September 16, 2002, is a true and accurate translation.

Dated: January 6, 2004

Respectfully submitted,

By Kazu Naito

Kazuhiko NAITO

[Title of the Invention]

QUINONE-BASED THERAPEUTIC AGENT FOR HEPATOPATHY

[Claims]

[Claim 1] An agent for treating or preventing hepatic disease containing menatetrenone as an active ingredient thereof.

[Claim 2] The agent according to claim 1, wherein the hepatic disease is hepatic cancer.

[Claim 3] The agent according to claim 2, wherein the hepatic cancer is des-γ-carboxy prothrombin (DCP) positive hepatic cancer.

[Claim 4] The agent according to any one of claims 1 through 3, wherein the agent improves prognosis after hepatic cancer treatment.

[Claim 5] The agent according to claim 4, wherein the agent is an agent that inhibits occurrence of portal venous invasion.

[Claim 6] An agent for inhibiting occurrence of portal venous invasion containing menatetrenone as an active ingredient thereof.

[Claim 7] An agent for improving survival rate after hepatic cancer treatment containing menatetrenone as an active ingredient thereof.

[Claim 8] An agent for inhibiting recurrence of hepatocellular carcinoma containing menatetrenone as an active ingredient thereof.

[Claim 9] An agent for reducing des-γ-carboxy prothrombin (DCP) level containing menatetrenone as an active ingredient thereof.

[Claim 10] A method of preventing portal venous invasion (PVI), comprising administering to a patient an effective dose of a medicine containing menatetrenone as an active ingredient thereof.

[Claim 11] A method of inhibiting recurrence of hepatocellular carcinoma, comprising administering to a patient an effective dose

of a medicine containing menatetrenone as an active ingredient thereof.

[Claim 12] A method of modulating the level of des-γ-carboxy prothrombin (DCP) in the blood of a patient, comprising administering to the patient an effective dose of a medicine containing menatetrenone as an active ingredient thereof.

[Claim 13] A use of menatetrenone for manufacturing an agent for inhibiting occurrence of portal venous invasion.

[Claim 14] A use of menatetrenone for inhibiting recurrence of hepatocellular carcinoma.

[Claim 15] An agent for treating or preventing hepatic disease containing a vitamin K as an active ingredient thereof.

[Detailed Description of the Invention]

[0001]

[Field of Industrial Utilization]

The present invention relates to an agent for treating or preventing hepatic disease, and more specifically to an agent for improving hepatic cancer prognosis, having menatetrenone as an active ingredient thereof.

[0002]

[Prior Art]

It is known that there is a high rate of portal venous invasion (hereinafter referred to as 'PVI') among hepatocellular carcinoma (hereinafter referred to as 'HCC') patients, and once PVI has occurred the prognosis is very poor. It is known that a high des-γ-carboxy prothrombin (hereinafter referred to as 'DCP') level in HCC patients

is closely linked to subsequent development of PVI (see Koike Y., Cancer 2001, 91:561-9). DCP is also called PIVKA-II (protein induced by vitamin K absence or antagonist II). DCP is a prothrombin that does not have normal coagulation activity, and is known to increase in level in the case of vitamin K (hereinafter referred to as 'VK') deficiency; DCP is thus a protein that is used as a marker for VK deficiency or impaired VK absorption.

Moreover, it has been reported that if VK is administered to HCC patients with a high DCP level, then the serum DCP level drops (see Cancer 1992, 69:31-8), and that upon administering vitamin K-II (hereinafter referred to as 'VK-II') to a DCP-producing HCC cell line *in vitro*, cell proliferation is inhibited (see Hepatology 1995, 22:876-82).

[0004]

[Problems to Be Solved by the Invention]

However, until now no clinical data had been collected with regard to it being possible, by administering VK-II to patients after HCC treatment, to inhibit the occurrence of PVI, and to inhibit the recurrence of hepatocellular carcinoma, thus improving the prognosis.

[0005]

In view of the above, it is an object of the present invention to provide an excellent agent for treating or preventing hepatic disease.

[0006]

[Means for Solving the Problem]

The present inventors accomplished the present invention by being the first to discover that administering an oral VK-II preparation to DCP-producing HCC patients contributes to inhibiting the occurrence of PVI after HCC treatment and improving the prognosis, and moreover inhibits the recurrence of hepatic cancer after treatment.

In other words, the present inventions provides

[1] an agent for treating or preventing hepatic disease containing menatetrenone as an active ingredient thereof;

[2] in the case of the above agent in [1], the hepatic disease is hepatic cancer;

[3] in the case of the above agent [2], the hepatic cancer is des-γ-carboxy prothrombin (DCP) positive hepatic cancer;

[4] according to any one of the [1] through [3], the above agent improves prognosis after hepatic cancer treatment;

[5] an agent for inhibiting occurrence of portal venous invasion (PVI);

[6] an agent for inhibiting occurrence of portal venous invasion (PVI) containing menatetrenone as an active ingredient thereof;

[7] an agent for improving survival rate after hepatic cancer treatment containing menatetrenone as an active ingredient thereof;

[8] an agent for inhibiting recurrence of hepatocellular carcinoma containing menatetrenone as an active ingredient thereof;

[9] an agent for reducing DCP level containing menatetrenone as an active ingredient thereof;

[10] a method of preventing portal venous invasion (PVI), comprising

administering to a patient an effective dose of a medicine containing menatetrenone as an active ingredient thereof;

[11] a method of inhibiting recurrence of hepatocellular carcinoma, comprising administering to a patient an effective dose of a medicine containing menatetrenone as an active ingredient thereof;

[12] a method of regulating the level of DCP in the blood of a patient, comprising administering to the patient an effective dose of a medicine containing menatetrenone as an active ingredient thereof;

[13] a use of menatetrenone for producing an agent for inhibiting occurrence of PVI;

[14] a use of menatetrenone for inhibiting recurrence of hepatocellular carcinoma; and

[15] an agent for treating or preventing hepatic disease containing a vitamin K as an active ingredient thereof.

[0007]

[Preferred Embodiments of the Invention]

Following is a more detailed description of the present invention through examples; however, the present invention is not limited to these examples.

[0008]

Hepatic cancer occurs with a high rate from chronic hepatitis and cirrhosis, which are targeted by the present invention, and having occurred hepatic cancer reoccurs after treatment with a high rate. For example, there are cases of cirrhosis developing from type C hepatitis or type B hepatitis, and there being recurrence after the tumors have been excised. According to the agent for

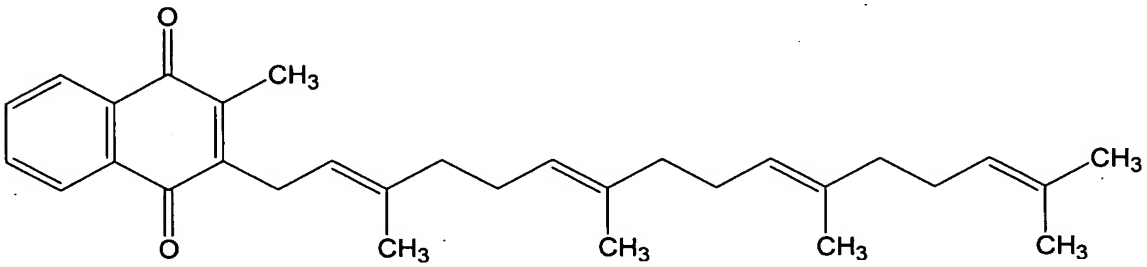
treating hepatic disease of the present invention, the prognosis after such hepatic cancer treatment can be improved very effectively (i.e. recurrence can be prevented or treated). Moreover, the occurrence of PVI, which is one form of recurrence of hepatic cancer with poor prognosis, can be inhibited very effectively.

[0009]

The menatetrenone used in the present invention has the chemical name 2-methyl-3-tetraprenyl-1,4-naphthoquinone, and has a structural formula as shown below.

[0010]

[formula 1]



[0011]

Menatetrenone is a yellow crystalline or oily substance, has no taste or odor, and is readily decomposed by light. Moreover, menatetrenone hardly dissolves in water. Menatetrenone is also called vitamin K-II (VK-II), and regarding the pharmacological action thereof, in the process of protein synthesis of blood coagulation factors (prothrombin, VII, IX, X), menatetrenone participates in the carboxylation reaction when glutamic acid residues are converted into physiologically active γ-carboxyglutamic acid, and menatetrenone promotes synthesis in the liver of normal prothrombin and so on, and activates the hemostasis

mechanism in a living body, thus physiologically realizing hemostasis.

[0012]

The menatetrenone that is the active ingredient in the medicine according to the present invention may be in the form of an anhydride or a hydrate. Moreover, menatetrenone has crystal polymorphs, but there is no limitation, with it being possible for the menatetrenone to be in any one of the crystal forms, or a mixture thereof. Furthermore, a metabolite produced through the menatetrenone according to the present invention being decomposed in a living body is also included in the scope of the claims of the present invention.

[0013]

The menatetrenone used in the present invention can be produced using a publicly known method, and as a representative example, can easily be produced using the method disclosed in Japanese Patent Application Laid-open No. 49-55650; alternatively, the menatetrenone can easily be procured from a chemical manufacturer. Moreover, the menatetrenone can be procured as a pharmaceutical preparation such as a capsule or an injection. Regarding the medicine of the present invention, the menatetrenone may be used as is, or may be made into a pharmaceutical preparation using a commonly used method by blending with ingredients that are commonly used as raw materials of medicinal preparations such as publicly known pharmaceutically permissible carriers and so on (e.g. excipients, binders, disintegrators, lubricants, colorants, flavorings,

stabilizers, emulsifiers, absorption promoters, surfactants, pH regulators, preservatives, antioxidants, etc.). Moreover, other ingredients such as vitamins and amino acids may be blended in as required. Examples of the form of the pharmaceutical preparation are tablets, a powder, granules, capsules, a syrup, suppositories, an injection, an ointment, a poultice, and so on.

[0014]

Moreover, in the present invention, there are no particular limitations on the form of administration of the menatetrenone, although oral administration is preferable. Menatetrenone capsules can be procured as Kaytwo capsules (proprietary name, made by Eisai Co., Ltd.) and Glakay capsules (proprietary name, made by Eisai Co., Ltd.), a menatetrenone syrup can be procured as Kaytwo syrup (proprietary name, made by Eisai Co., Ltd.), and an injection can be procured as Kaytwo N (proprietary name, made by Eisai Co., Ltd.).

[0015]

The menatetrenone-containing medicine according to the present invention is useful for treating or preventing hepatic disease. A preferable dose of the menatetrenone is generally 10 to 200 mg/day, more preferably 30 to 135 mg/day.

[0016]

Examples

Trial examples of the present invention are given below; however, these trial examples are merely illustrative, and the present invention is not limited thereto. A person skilled in the art could implement the present invention not only through the trial

examples shown below, but also with any of various modifications within the scope of the claims appended to the specification of the present application, and such modifications are deemed to be included in the scope of the claims of the present application.

Trial Example 1

A clinical trial (randomized prospective controlled study) was carried out as follows.

[0017]

Out of patients with hepatocellular carcinoma, ones having a serum DCP level above 60 IU/L (DCP positive hepatic cancer) were included in the trial. On the other hand, patients having portal venous invasion, and patients in which there was already VK metabolism through administration of VK or an anti-VK agent, were excluded from the trial. The details of the trial were as shown in Table 1.

[0018]

Table 1

Trial subjects
Subjects included
1. Hepatic cancer patients
2. Serum DCP level ≥ 60 IU/L
Subjects excluded
1. Portal venous invasion
2. Cancer metastasize out of liver
3. uncontrolled ascites
4. Bilirubin > 3.0 mg/dl

5. Taking vitamin K preparation, warfarin

Group administered VK-II

Took 45 mg of vitamin K-II (Glakay) three times after hepatic cancer treatment

Group not administered VK-II

Hepatic cancer treatment only

Judgement criteria

1. Occurrence of portal venous invasion

2. Death

[0019]

FIG. 1 shows a selection flowchart of the patient. 126 hepatic cancer patients were given treatment from February 1999 to November 2001. As the hepatic cancer treatment, percutaneous cauterization therapy (RFA and/or PEIT) for HCC, treatment via the blood vessels (TAE or TAI), or surgical excision was carried out. Of the patients, 5 were excluded from the present trial.

[0020]

Next, the remaining 121 patients were randomly divided into a treated group (n = 60) and an untreated group (n = 61). The treated group were orally administered 45 mg/day of VK-II (proprietary name Glakay, made by Eisai Co., Ltd.) after the hepatic cancer treatment, while the untreated group were not administered VK-II.

[0021]

Follow-up tests were carried out after the hepatic cancer treatment. As the follow-up tests, ultrasonography (abdominal

echography) was carried out every 3 months, a CT scan was carried out every 6 months, and the levels of the tumor markers alpha-fetoprotein and DCP were measured every one month.

[0022]

Table 2 shows the profile of the patients. No important differences were found in any of the clinical parameters between the treated group and the untreated group.

[0023]

Table 2

Patients Profile

	Treated group (n = 60)	Untreated group (n=61)	P
Age	66.9±7.0	67.3±7.5	.8
Sex (male/female)	36/24	45/16	.12
Virus (HCV/non HCV)	50/10	52/9	.81
Tumor size (mm)	32±11	35±18	.27
Number of tumors	4.0±3.2	4.3±3.5	.66
Child class (A/B or C)	18/42	27/34	.13
Albumin (g/dl)	3.4±0.5	3.5±0.5	.3
Bilirubin (mg/dl)	1.2±0.7	1.1±0.9	.4
ALT (IU/L)	55±38	61±47	.47
Prothrombin (%)	78±16	78±14	.99
Blood platelets ($10^4/mm^3$)	10.8±6.0	11.5±6.6	.52
AFP (ng/L)	2668±7666	1539±7036	.42
DCP (IU/L)	985±2639	1178±5108	.80
PTA with/without	48/12	41/20	.15

average ± SD (Median)

[0024]

FIG. 2 shows a graph indicating changes in the DCP level in the serum. The solid line is for the treated group, and the dashed line is for the untreated group. For both the treated group and the untreated group, the DCP level dropped after the hepatic cancer treatment. Subsequently, the DCP level remained approximately constant for 12 months for the treated group, whereas the DCP level

gradually increased for the untreated group.

[0025]

FIG. 3 shows a graph indicating changes in the PVI incidence rate. As shown in FIG. 3, for the treated group, the PVI incidence rate was 2% after 1 year, and 23% after 2 years. On the other hand, for the untreated group, the PVI incidence rate was 23% after 1 year, and 47% after 2 years ($P = 0.018$).

[0026]

FIG. 4 shows a graph indicating changes in the survival rate. As shown in FIG. 4, the survival rate after 2 years was 66% for the treated group, but 28% for the untreated group ($P = 0.044$).

[0027]

Statistical analysis was carried out on the PVI incidence rate and the survival rate for the two groups. That is, calculations were carried out using the Cox proportional hazard model, and a test was carried out using the log-rank method. The average observation period was 12 ± 8 months.

[0028]

From the above results, it is suggested that by orally administering a VK-II preparation, incidence of PVI in DCP positive HCC patients is suppressed very effectively, and moreover survival rate is greatly increased, and hence the prognosis after hepatic cancer treatment is markedly improved.

Trial Example 2

A trial was carried out as follows with an objective of investigating the effect and safety of VK-II in inhibiting recurrence

of hepatocellular carcinoma after treatment.

61 cases in which hepatocellular carcinoma was diagnosed and then after treatment therefor necrosis (or curative excision) was judged by contrast CT to have completely occurred were entered from March 1999 to March 2001, the entered cases were divided into two groups, namely a VK-II-administered group for which the end of the patient ID number was an odd number and a non-administered group (control group) for which the end of the patient ID number was an even number, and a VK-II preparation (proprietary name Glakay, made by Eisai Co., Ltd.) was orally administered at a dose of 45 mg/day to the administered group. Contrast CT or MRI was carried out every 3 months, and a statistical analysis of the time period until recurrence was carried out. Specifically, comparison was carried out using the Kaplan-Meier method (log-rank test), and the risk ratio for recurrence was analyzed using the Cox proportional hazard model.

[0029]

As shown in Table 3, the average observation period for the 61 entered cases (32 cases in the administered group, 29 cases in the non-administered group) was 19.6 months (7-32).

[0030]

Table 3

Subjects	Administered group(32 cases)	Control group(29 cases)
Age	63.3±7.5(48-75)	64.5±6.7(45-74)
Sex (male/female)	23/9	18/11
Cause of disease (type C/type B/type B+C)	28/3/1	26/2/1
History of alcohol consumption (addict/non-addict)	10/22	3/26
First occurrence/recurrence	15/17	14/15
Tumor size (mm)	17.7±5.1(10-30)	19.4±6.9(10-38)
Number of tumors	1.50±0.88(1-4)	1.48±0.74(1-3)
Log AFP (ng/ml)	1. 47±0.61 (0.60-3.09)	1. 72±0.91 (0.48-3.88)
PIVKA-II (mAU/ml)	41.8±65.4 (8-346)	70.3±104.1 (7-417)
Liver function (LD A/B/C)	15/16/1	13/15/1
Treatment method (excision/non-excision)	1/31	3/26
Average observation period (months)	24.3±7.1(13-37)	24.2±8.3(12-37)

[0031]

Upon calculating cumulative recurrence rates, the 1-year recurrence rate was found to be 12.5% for the VK-II-administered group and 55.2% for the control group, and the 2-year recurrence rate was found to be 39.6% for the VK-II-administered group and 85.5% for the control group. From these results, it was found that the hepatic cancer cumulative recurrence rate was statistically significantly suppressed for the VK-II-administered group compared with the control group.

[0032]

FIG. 5 shows a graph indicating the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence). As shown in FIG. 5, the time period until 50% recurrence was 26 months for the VK-II-administered group, but was 10 months

for the control group.

[0033]

Moreover, upon calculating the hepatic cancer cumulative recurrence rates considering only HCV cases (type C hepatitis cases), the 1-year recurrence rate was found to be 7.1% for the VK-II-administered group and 61.5% for the control group, and the 2-year recurrence rate was found to be 37.8% for the VK-II-administered group and 87.2% for the control group. From these results, it was found that, even when considering only HCV cases, the hepatic cancer cumulative recurrence rate was statistically significantly suppressed for the VK-II-administered group compared with the control group.

[0034]

FIG. 6 shows a graph indicating the results for the HCV cases only in the trial to verify the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence). As shown in FIG. 6, the time period until 50% recurrence was 26 months for the VK-II-administered group, but was 10 months for the control group.

[0035]

FIG. 9 shows a diagram indicating the results of analyzing the risk ratio (RR) for recurrence using the Cox proportional hazard model. As shown in FIG. 9, taking the risk ratio for recurrence of hepatic cancer to be 1 for the control group, this risk ratio is approximately one third of that at 0.329 for the VK-II-administered group; in particular, considering only the HCV cases, the risk ratio

becomes 0.210, i.e. is reduced to approximately one fifth, by administering VK-II.

[0036]

FIG. 7 shows a graph indicating the results in the case of excluding cases of local recurrence in the trial to verify the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence) (VK-II-administered group: 29 cases, non-administered group: 22 cases). Moreover, FIG. 8 shows a graph indicating the results in the case of excluding cases of recurrence within 6 months in the trial to verify the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence) (VK-II-administered group: 31 cases, non-administered group: 22 cases). As shown in FIGS. 7 and 8, in these cases, again the hepatic cancer cumulative recurrence rate was statistically significantly suppressed for the VK-II-administered group compared with the control group.

[0037]

FIG. 10 shows graphs indicating the results of analyzing the DCP level before treatment and upon recurrence. As shown in FIG. 10, with all of the cases of recurrence in the VK-II-administered group, DCP was negative, and moreover there were no side effects, and there were no dropout.

[0038]

It should be noted that PIVKA-II is also called DCP, which is typical tumor marker in the field of hepatocellular carcinoma, such as impaired vitamin K absorption.

[0039]

The menatetrenone-containing agent for treating hepatic disease according to the present invention has an excellent effect of inhibiting occurrence of PVI with hepatic disease, in particular DCP positive hepatic cancer, and moreover has an excellent effect of improving the prognosis after hepatic cancer treatment. Furthermore, the menatetrenone-containing agent for treating hepatic disease according to the present invention is very useful in inhibiting recurrence of hepatic cancer after treatment.

[Brief Description of Drawings]

FIG. 1 shows a selection flowchart of the patient.

FIG. 2 shows a graph indicating changes in DCP level in serum.

FIG. 3 shows a graph indicating changes in PVI incidence rate.

FIG. 4 shows a graph indicating changes in survival rate.

FIG. 5 shows graph indicating the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence).

FIG. 6 shows a graph indicating results for HCV cases only in the trial to verify the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence).

FIG. 7 shows a graph indicating results in the case of excluding cases of local recurrence in the trial to verify the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence).

FIG. 8 shows a graph indicating results in the case of excluding

cases of recurrence within 6 months in the trial to verify the effect of VK-II administration on hepatic cancer recurrence inhibition (50% recurrence).

FIG. 9 shows a diagram indicating results of analyzing the risk ratio (RR) for recurrence using a Cox proportional hazard model.

FIG. 10 shows graphs indicating results of analyzing the DCP level before treatment and upon recurrence.

[Abstract]

[Problem]

Since a useful agent for treating a hepatic disease until the present time, the object of the present invention is to provide the agent for treating the hepatic disease by inhibiting occurrence of portal venous invasion.

[Means for Solution]

There is disclosed an agent for treating or preventing hepatic disease containing menatetrenone as an active ingredient thereof. This agent for treating or preventing hepatic disease is effective against hepatic cancer, in particular DCP (des-γ-carboxy prothrombin) positive hepatic cancer. Moreover, the agent for treating or preventing hepatic disease containing menatetrenone as an active ingredient thereof according to the present invention exhibits remarkable effects in improving the prognosis after hepatic cancer treatment, and exhibits excellent effects as an agent for inhibiting the recurrence of hepatic cancer.

FIG.1

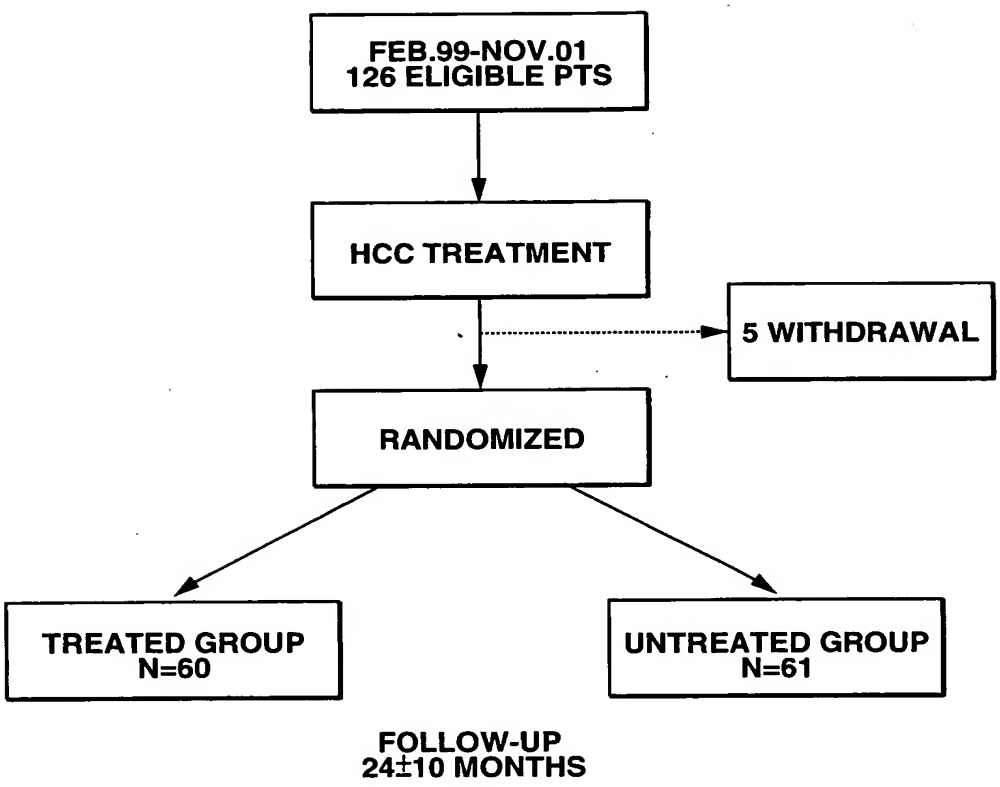


FIG.2

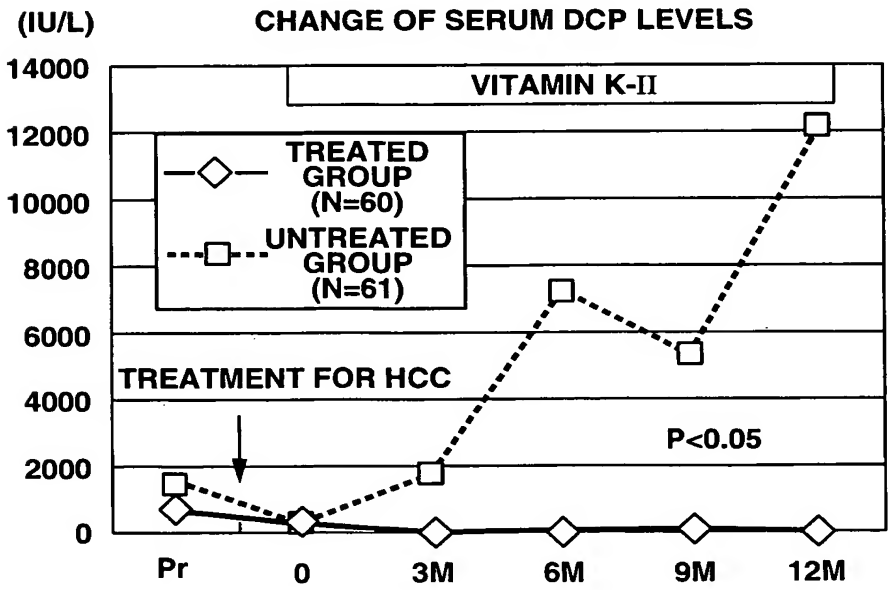
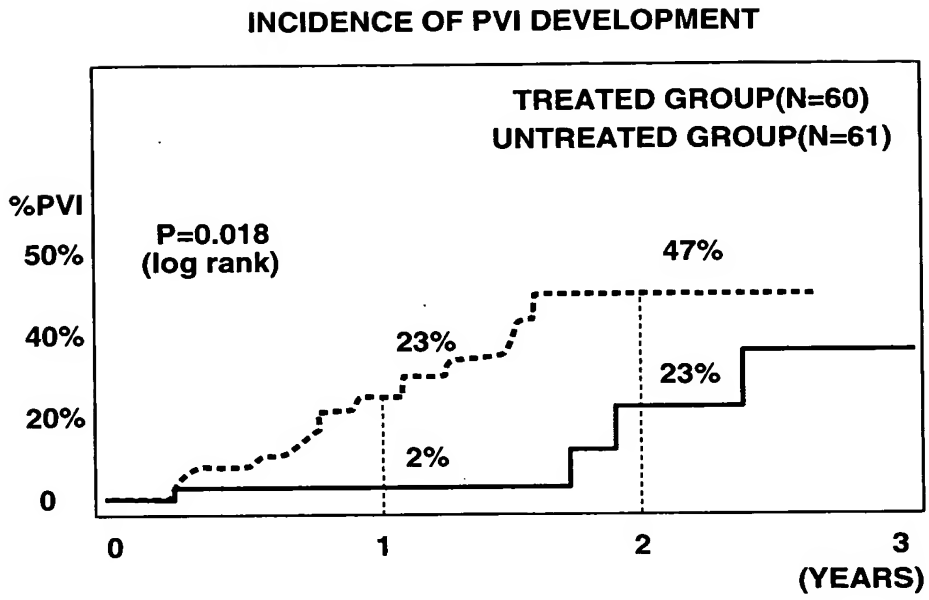


FIG.3


INCIDENCE OF PVI DEVELOPMENT
TREATED GROUP(N=60)
UNTREATED GROUP(N=61)
%PVI
50%
40%
20%
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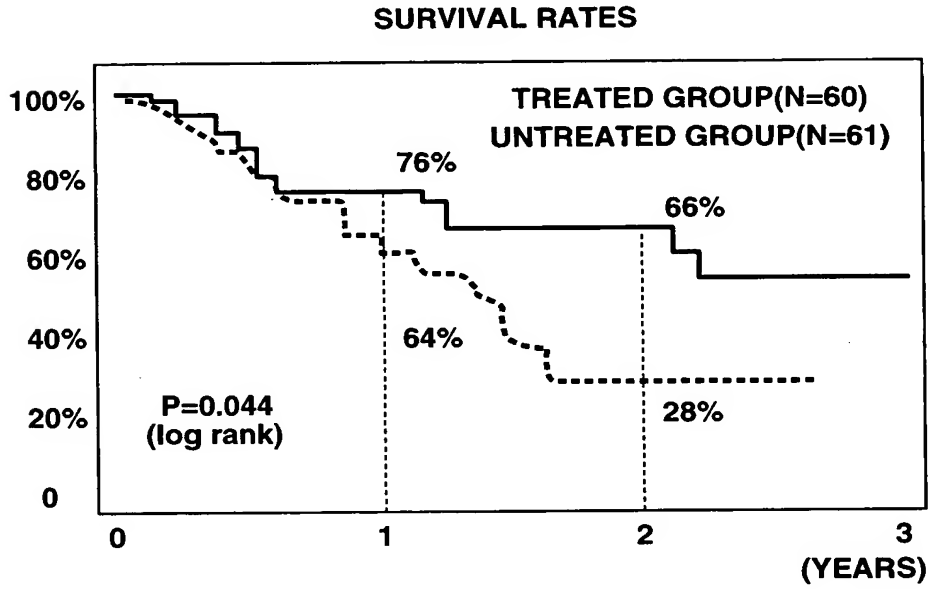
(log rank)
47%
23%
23%
2%
0
1
2
3
(YEARS)

FIG.4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40%
20%
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UNTREATED GROUP(N=61)
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64%
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(log rank)
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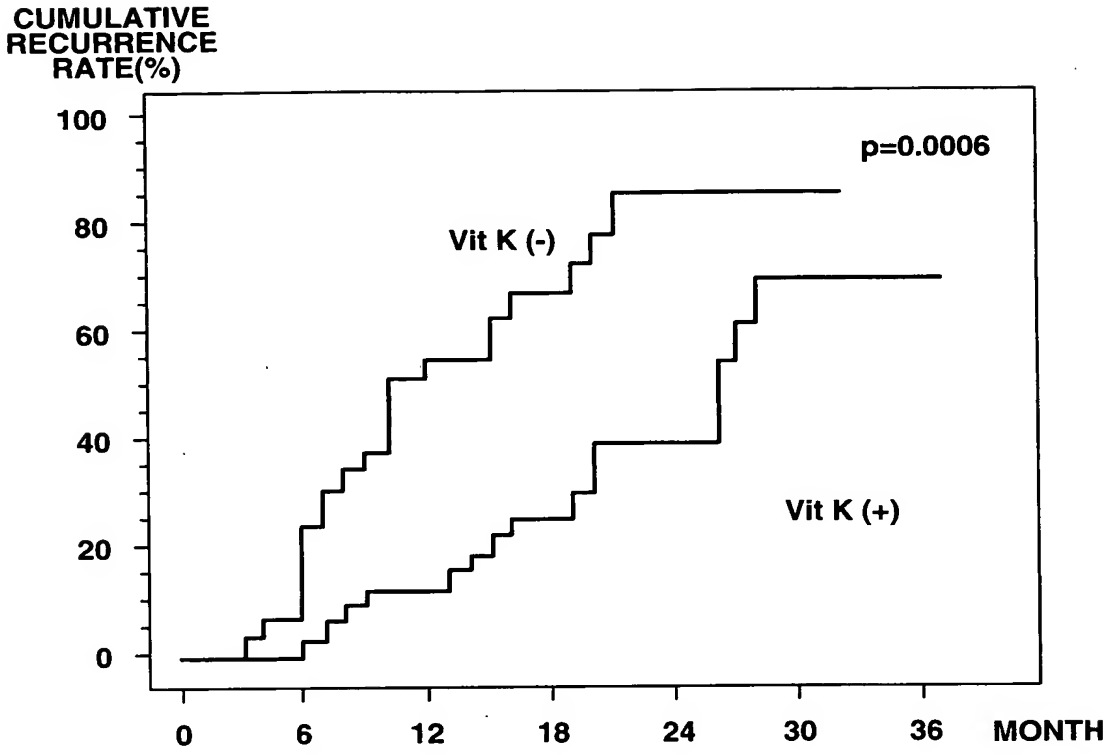
1
2
3
(YEARS)

FIG.5


CUMULATIVE RECURRENCE RATE(%)
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80
60
40
20
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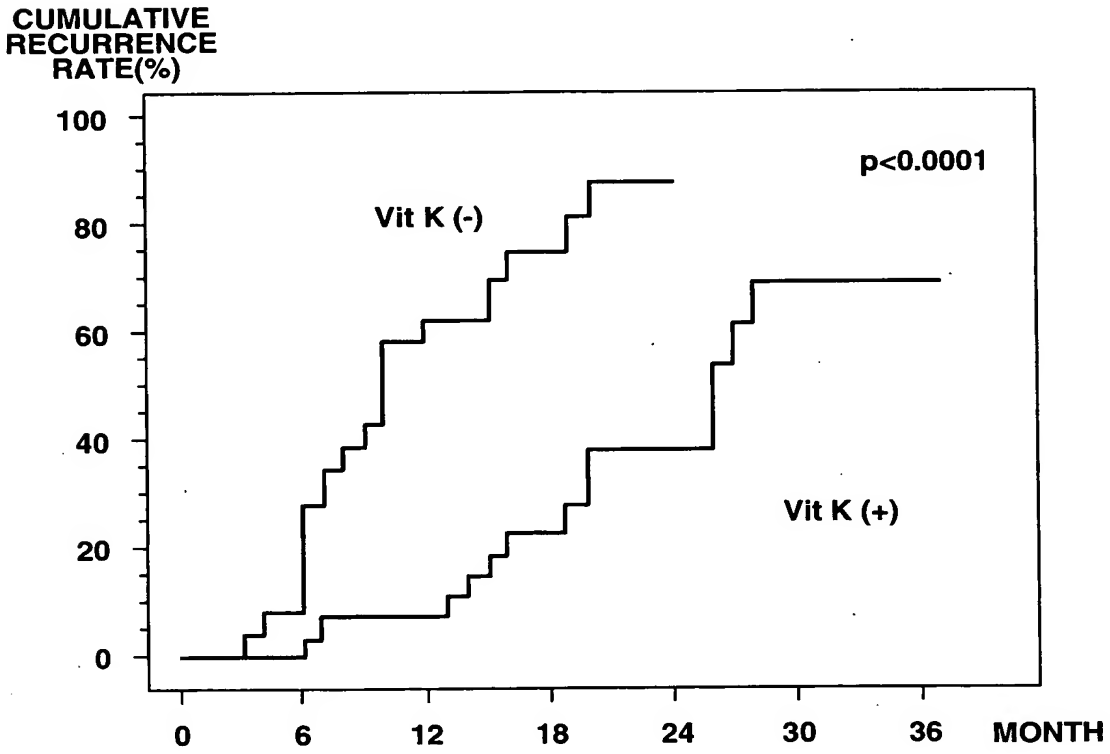
p=0.0006
Vit K (-)
Vit K (+)
0
6
12
18
24
30
36
MONTH

FIG.6


CUMULATIVE RECURRENCE RATE(%)
100
80
60
40
20
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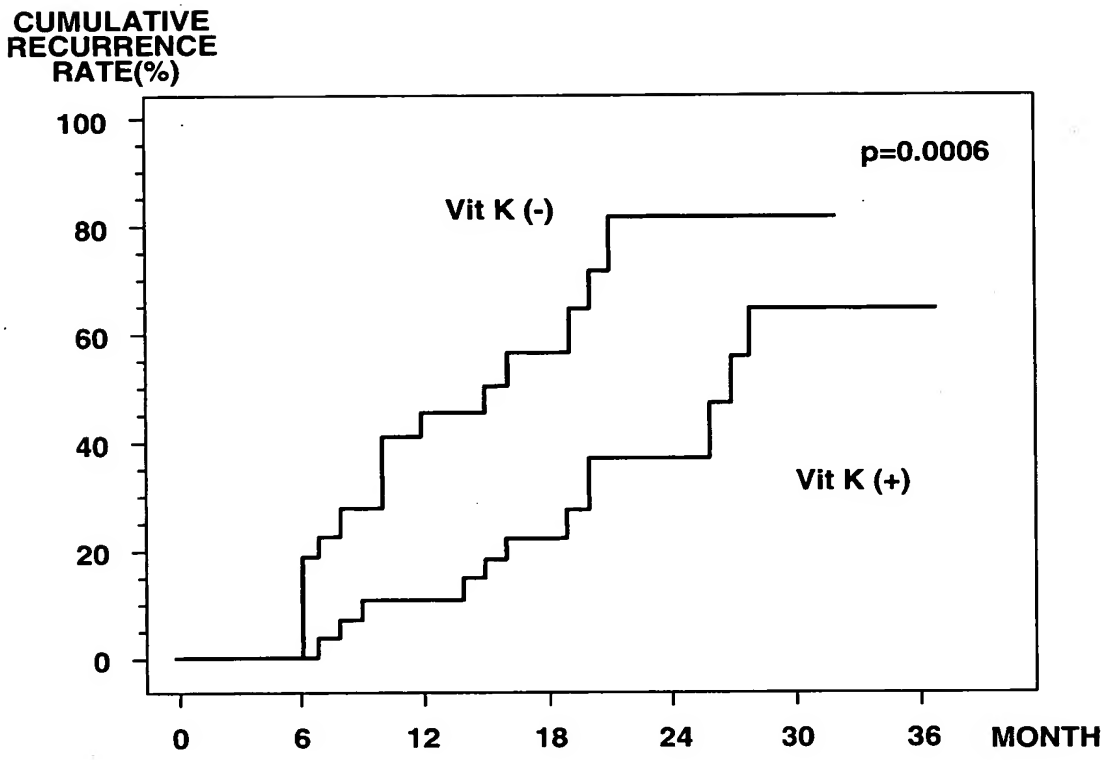
p<0.0001
Vit K (-)
Vit K (+)
0
6
12
18
24
30
36
MONTH

FIG.7


CUMULATIVE RECURRENCE RATE(%)
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60
40
20
0
p=0.0006
Vit K (-)
Vit K (+)
0
6
12
18
24
30
36
MONTH

FIG.8

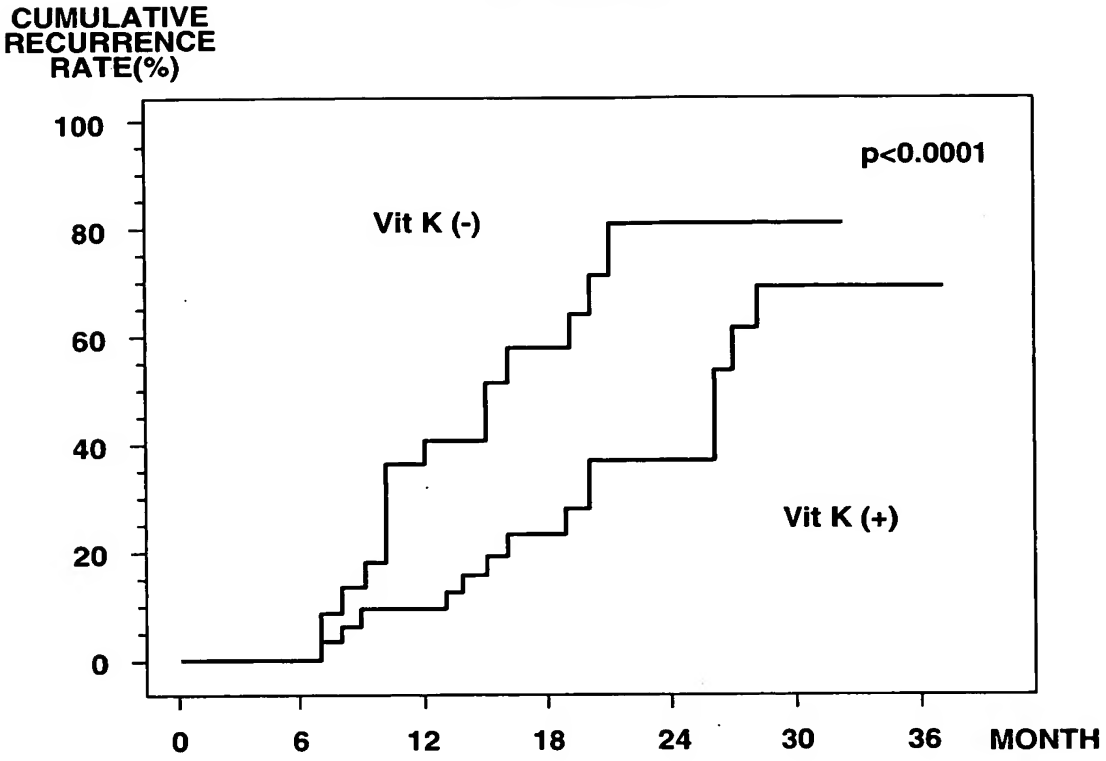
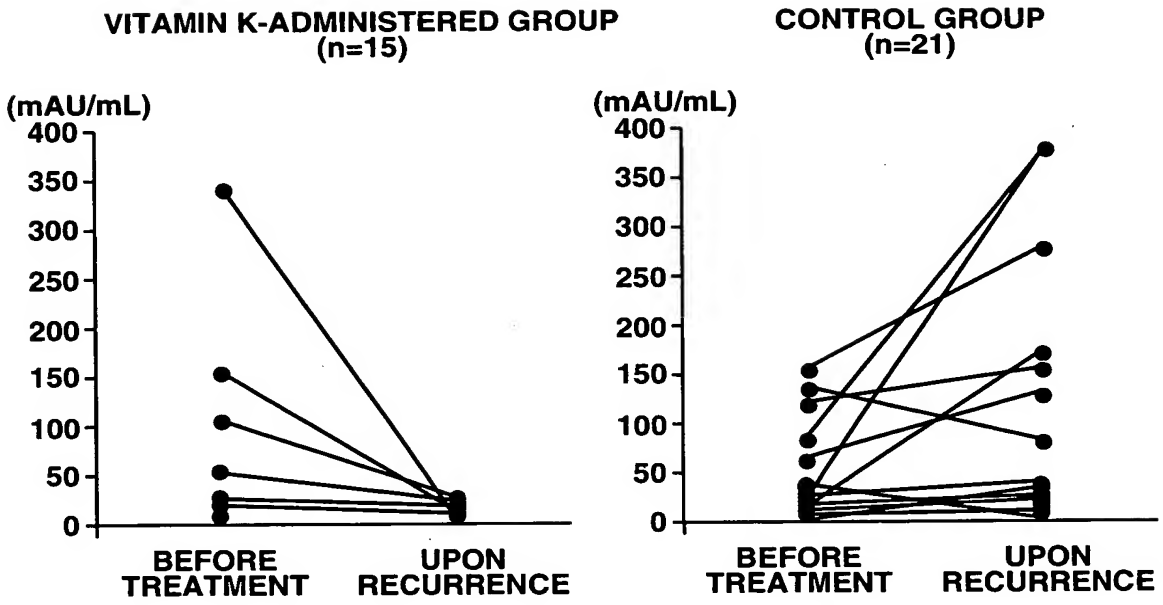


FIG.9

RISK RATIO (RR) FOR RECURRENCE OF HEPATIC CANCER ACCORDING TO COX PROPORTIONAL HAZARD MODEL

		RR	p	95% C.I
ALL CASES	VK-Ⅱ NOT ADMINISTERED	1		
	VK-Ⅱ ADMINISTERED	0.329	0.0013	0.167-0.648
HCV CASES	VK-Ⅱ NOT ADMINISTERED	1		
	VK-Ⅱ ADMINISTERED	0.210	0.0001	0.094-0.468

FIG.10


VITAMIN K-ADMINISTERED GROUP
(n=15)
(mAU/mL)
400
350
300
250
200
150
100
50
0
BEFORE TREATMENT
UPON RECURRENCE
CONTROL GROUP
(n=21)
(mAU/mL)
400
350
300
250
200
150
100
50
0
BEFORE TREATMENT
UPON RECURRENCE